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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
NASHED, NASHAAT T

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/724,876	Applicant(s) Julien et al.
	Examiner Nashaat T. Nashed	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 13, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *15-20, 24, and 25* is/are pending in the application.

4a) Of the above, claim(s) *18-20 and 25* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *15-17 and 24* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *11 & 15*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election with traverse of Group V, claims 15-17, 19, 25 and 25, drawn to modified epoD, in Paper No. 13 is acknowledged. The traversal is on the ground(s) that claim 15 is drawn a modified functional epothiolone polyketide synthase (PKS), not an individual, arbitrarily chosen reading frames and that there is no point of making in making a modification of a single open reading frame that is a part of a PKS. Applicants arguments have been fully considered, but they are found unpersuasive. Claim 15 encompasses an improper Markush Group comprising the epothiolone polyketide synthaes the product of *epoA-epoE* genes. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.) The products of *epoA-epoE* do not share a common utility or a common structural feature required for said utility. The products of *epoA-epoE* are polyketide synthases and not a polyketide synthase each of which catalyzes the formation of different product from different starting material and having different structure. Examining Groups I-V represent a search burden on the examiner because each of the open reading frame has to be searched in the patent and non-patent literature. Applicants should keep in mind the epoA-epoE are huge proteins, e. g., epoD is 7257 amino acid, each of which comprises large number of enzymatic activity wherein each enzymatic activity is comprised in a domain that can functional independently or in a chimeric polyketide synthase, see claims 24 and 25.

The requirement is still deemed proper and is therefore made **FINAL**.

Claims 15-17, and 24 are under consideration as they relate to the epoD. Claims 18 and 20 remain withdrawn from further consideration by the examiner. Also, claims 19 and 25 are withdrawn from further consideration by the examiner because they do not contain elected subject matter related to epoD.

This application appears to have been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim 15-17, and 24 are objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush groups. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.). The claims are directed to a modified epothiolone polyketide synthase. The specification identified five epothiolone polyketide synthases each of which have a different structure and function.

The claims are objected to because they contain non-elected subject matter. Correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-17, and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) claims 15-17, and 24 contain the undefined abbreviations and acronyms PKS, AT, KR, DH, ER, and MT. Abbreviations and acronyms must be defined at least once in the claims. For examination purposes only, it is assumed that the meaning of the abbreviation are: (a) PKS: polyketide synthase, (b) AT: acyltransferase, (c) KR: ketoreductase, and (d) ER: enoylreductase.

(b) The phrases "modified functional epothilone PKS", "inactivation of the NRPS-like module 1, or KS2 catalytic domain", and replacement of the NRPS module 1 with an NRPS of different specificity" in claim 15 render the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The phrase "modified functional epothilone PKS" is indefinite because there are five different epothiolone synthases. The claim is confusing because epoD does not have NRPD domain or KS2. For examination purposes only, the phrase is assumed to mean the epoD polyketide synthase. The other phrases are deleted from the claim because they are drawn to non-elected subject matter.

(c) The phrases "proteins of a non-epothilone PKS", "or proteins of epothilone PKS" in claim 24 render the claim indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. For examination purposes, the phrase "proteins of a non-epothilone PKS" is assumed to mean "a catalytic or a functional domain from a polyketide synthase other than those from the biosynthetic pathway of epothilone. Similarly the phrase "or proteins of epothilone PKS" is assumed to mean "a catalytic or functional domain from the polyketide synthases epoA-epoE.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15-17 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schupp *et al.* (Schupp, IDS paper number 11, Ref.No. 11: U. S. Patent 6,121,029) in view Khosla *et al.* (Khosla A, U. S. Patent 6,391,594) and Khosla *et al.* (Khosla B, IDS paper number 11, Ref No. 33: WO 97/02358).

Schupp teach the gene cluster for the biosynthesis of epothilones from *Sorangium cellulosum* (SEQ ID NO: 1), see the abstract. They identified 22 open reading frames in the nucleic acid sequence of SEQ ID NO: 1 which are listed in Table 1, see the Table bridging column 30 and 31. In particular, they identified an open reading frame corresponds to residues 21,746-43,519 which they call epoC encoding the 7,257 amino acid of SEQ ID NO: 5 and containing four modules, see column 33, lines 7-61. Also, they identified all catalytic and functional activities of the epoC gene products, see column 33, lines 7-61. The epoC gene taught by Schupp appears to be identical or functionally equivalent to the epoD of the instant application. The sequence homolgy between the two nucleic acid sequences is >98%. In addition, they teach the recombinant expression of epothilone gene cluster in a host cell such as *Streptomyces coelicolor*, example 13 and the isolation of epothilone from the host cell culture, see example 14. In addition, they teach that epothilone have narrow antifungal spectrum and mimic the activity of taxol as an anticancer agents, see column 2, lines 45-67.

Khosla A teach the modification of polyketide synthases using to produce new derivatives of polyketides. Example 2 teaches the replacement of DEBS modules by rapamycin modules and the replacement of DEBS AT2 domain by rapAT2 domain. Example 3 teach the deletion of β-carbonyl modifying activity. Example 5 teaches manipulation of macrolide ring size by inserting a thioesterase after the last module of the biosynthetic pathway. In each modification, a new polyketide compound is obtained.

Khosla B teach a cell free system for the synthesis of polyketides from modified DEBS, see in particular example 7.

Schupp and Khosla A provide one of ordinary skill in the art with motivation at the time of invention to modify an epothilone polyketide synthase. Schupp teach the antifungal and anticancer activities of epothilone derivatives. Khosla A teach that the modification of a polyketide synthase produces new derivatives of polyketides which can be made by

a designed biosynthetic pathway. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to obtain the nucleic acid sequence encoding epoD as taught by Schupp, replace the AT domain by another having different specificity, inactivate β-carbonyl modifying activity or add additional β-carbonyl modifying activity by the teaching of Khosla A (claim 15). Once the ordinary skill in the art obtained the nucleic acid encoding the modified epoD, he/she would have inserted the nucleic acid sequence into a host cell, expressed the modified epoD, isolated the epoD and utilized the modified epoD in an *in vitro* method such as that taught by Khosla B to make novel epothiolone. The method would have included other polyketide synthases and other modifying enzymes from the epothilone biosynthetic pathway taught by Scupp (claims 16 and 17). Similarly, one of ordinary skill in the art would have been further motivated by the teaching of Khosla A to use the four modules and and the many domains of the epoD to modify the DEBS polyketide synthase to obtain new derivatives and analogs of 6-DB. Thus, the ordinary skill in the art would use the teachings of Khosla A to generate new modified DEBS in order to use them in a method to make new molecules (claim 24). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nashaat T. Nashed, Ph. D.
Primary Examiner